REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the remarks which follow. Claims 29-42 have been amended to recite the "inclusion complex". This amendment is supported in the application as filed. The claims presently pending in the application are claims 29-44, inclusive.

Claims 29 and 34-42 stand rejected under 35 U.S.C. §102(b) as being anticipated by Ronsen et al. (WO 99/16440). This rejection is respectfully traversed.

As stated by the Examiner, Ronsen et al. are silent about "*the nature of complexation*", better still, about the interaction between paroxetine with cyclodextrins or derivatives thereof. Therefore, claims 29-42, which have been amended herewith to recite the nature of the claimed complex, i.e. an *inclusion complex*, distinguishes over the teaching of Ronsen et al. and serves to overcome the §102(b) rejection.

Since dependent claims 43 and 44 depend directly or indirectly from independent claim 29, they, too, distinguish over Ronsen et al., and, thus, the §102(b) rejection should be withdrawn.

The differences between the claimed inclusion complex and the products described by Ronsen et al. are supported by the experimental data reported in the present application in comparison with the data reported by Ronsen et al.

In fact, the amorphous paroxetine hydrochloride and hydroxypropyl-β-cyclodextrin composition according to Example 5 of Ronsen et al. has been subjected to Differential Scanning Calorimetry (hereinafter referred to as DSC), and the results are reported in Figure 7. The thermogram in Figure 7 shows a well defined peak at a temperature of approximately 175°C and a smaller peak at a temperature of approximately 145°C.

In contrast, from an examination of the thermogram obtained by Applicant in a DSC test carried out on a complex between paroxetine hydrochloride and hydroxypropyl-β-cyclodextrin, prepared according to the invention, is reported in Figure 6 of the present application. In this case, the absence of any peak at a temperature of approximately 175°C is immediately evident.

The profiles of the two (2) thermograms are completely different, thus proving that the claimed paroxetine complexes are distinguishable from the paroxetine compositions containing the cyclodextrins disclosed by Ronsen et al.

Finally, the formation of an inclusion complex has been shown by Applicant by means of the NMR analysis carried out on some of the products which were prepared. (See Example 12 B), pages 11-13. As shown at Table 3 at page 13, in the presence of paroxetine, a down-field change is observed in the chemical shift of the protons of the inner surface of the cavity of β-cyclodextrin, indicating an interaction with paroxetine and, therefore, the existence of an inclusion complex.

The Examiner has rejected claims 29 and 34-44 under §103(a) as obvious in view of Ronsen et al., and further in view of Benneker et al. (US 5,874,447). This rejection is respectfully traversed.

In view of the amendments to the claims, the differences between the cited prior art and the claimed invention should now be evident. The claimed invention relates to *an inclusion complex* of paroxetine with cyclodextrin or derivatives thereof, whereas "*Ronsen et al. discloses paroxetine stabilised by being combination with a hydroxyl-containing compound*", as affirmed by the Examiner.

The reasons why the differences between the products disclosed by Ronsen et al. and the claimed inclusion complexes would have been unobvious to one of ordinary skill in the art at the time the invention was made are set forth below.

As reported in the present application, at page 2, last paragraph, "*paroxetine as free base is unsuitable to be used as such for the manufacturing of pharmaceutical forms as it consists of dense liquid having oily characteristics or of a waxy solid. Moreover, it easily decomposes becoming oxidised and its solubility in water is very low*". The scope of the present invention is to solve these problems.

The Applicant has found that the present inclusion complexes have a high chemical stability, an improved solubility in water, are suitable for the preparation of liquid or solid pharmaceutical compositions based on paroxetine, and demonstrate for the included paroxetine a dissolution behaviour which is independent of pH.

Ronsen et al., besides being silent on the inclusion complexes of paroxetine with cyclodextrin or derivatives thereof, is also silent about the utility of paroxetine complexation in the terms above reported.

In his first Office Action of February 12, 2003, at page 6 thereof, third full paragraph, line 4, the Examiner noted that "*Ronsen teaches that complexation of the paroxetine with a hydroxyl-bearing compound produces more easily handled non-hygroscopic, amorphous product. See page 2, lines 21-34*".

As a matter of fact, Ronsen et al. teach that compositions of amorphous paroxetine hydrochloride and a hydroxyl-bearing compound, generate a non-hygroscopic formulation of paroxetine.

Thus, the Ronsen et al. reference notes the utility of interaction between paroxetine and hydroxyl-bearing compounds with respect to hygroscopicity, but it is silent about the

utility of paroxetine complexation by inclusion in cyclodextrins in respect to the problems of obtaining a paroxetine formulation having a high chemical stability, an improved solubility in water, or a dissolution behaviour which is independent of pH.

Finally, in order to assess the non-obviousness of the claimed invention, it is relevant to consider that Ronsen et al. teach the preparation of compositions of paroxetine with hydroxyl-bearing compounds, such as carboxylic acids and hydroxy derivatives thereof, sugar acids, polyhydric acids, citric acid and, among this plethora of compounds -- a veritable laundry list --that in no way could yield an inclusion complex, also cyclodextrins.

In view of the foregoing, it would therefore be entirely unobvious to one of ordinary skill in the art at the time the invention was made, to prepare an inclusion complex of paroxetine and cyclodextrins to try to solve the aforesaid technical problems.

The Examiner also cites the prior art document US 5,874,447, hereinafter referred to as Benneker et al., which teaches paroxetine in the form of a free base, in the form of salts including those salts disclosed by the present application, and of hydrates of paroxetine derivatives.

Nevertheless, Bennaker et al. do not teach, disclose, or even suggest the preparation of an inclusion of paroxetine and cyclodextrins. Accordingly, Bennaker et al. do not render the claimed invention obvious, either when taken alone or in combination with the teachings of Ronsen et al.

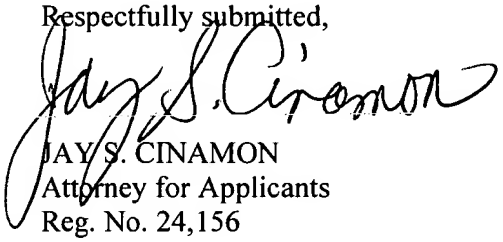
It is, therefore, respectfully submitted that the claims distinguish over the combination of Rosen et al. and Bennaker et al. Accordingly, since a *prima facie* case of obviousness has not been established, the §103(a) rejection has been overcome and should be withdrawn.

The unobviousness of the present inclusion complexes as claimed in claims 29-42 also supports the unobviousness of the pharmaceutical compositions containing the inclusion complex as the active principle, claimed in present claims 43 and 44.

The issuance of a Notice of Allowance is, accordingly, respectfully solicited.

Please charge any fees which may be due to our Deposit Account No. 01-0035.

Respectfully submitted,



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